An Improved Synthesis of Methyl 1,3-Dihydro-2H-pyrrolo[3,4-b]quinoline-2-carboxylate

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Abstract: Optimization of an old route leads very easily, in four steps, to methyl 1,3-dihydro-2H-pyrrolo[3,4-b]quinoline-2-carboxylate in 45% yield from commercial starting materials. This procedure can be compared to recently described methods whose yields were only 23–28% and required five to seven steps from advanced intermediates and chromatographic purifications. Moreover, using this method, the title compound can now be obtained in large quantities.

Key words: heterocycles, quinolines, pyrrolidinones, Friedländer condensation, 1,3-dihydro-2H-pyrrolo[3,4-b]quinolines

Ethyl 1,3-dihydro-2H-pyrrolo[3,4-b]quinoline-2-carboxylate (1a) is a key compound in several syntheses of camptothecin or acuminatine derivatives, mappicine ketone, inhibitors of human cathepsin K and L, inhibitors of PI3-kinase related kinases (PIKKs). One starting point for the synthesis of heterocycle 1a is 2,3-dihydroxyquinoline, which is obtained by oxidation of acridine or by reaction of 2-aminobenzaldehyde with dimethyl acetylenedicarboxylate.

Heterocycle 1a can also be prepared by reacting aniline with ketoester via cyclization into a quinolone and then reduction of the chloro intermediate. A [4+1] radical annulation and a [4+2] cycloaddition of propargylated intermediates have also been shown to give 1a derivatives.

Another synthesis of quinoline 1a involves the Friedländer condensation of 2-aminobenzaldehyde (5a) in the presence of p-toluenesulfonic acid, in a melt at 195–240 °C for five minutes. As part of a project on new camptothecin derivatives, we needed a convenient synthesis of carbamate 1a derivatives. We had been concentrating on the sequence shown in Scheme 1, but found it necessary to greatly improve a number of different steps in order to get the best reproducibility for intermediates 2a and 3a, and to obtain carbamate 1a in a purer state. Thus, we wish to report here the optimization of these syntheses; in order to monitor the reactions by 1H NMR, it was found opportune to use compounds substituted by methyl ester groups instead of the ethyl groups as depicted in Scheme 1.

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75% yield,\textsuperscript{10} with no chromatographic purification necessary.\textsuperscript{2} In the same way as described for 2a,\textsuperscript{2} partial hydrolysis of 2b in dilute hydrochloric acid easily furnished pure pyrrolidinone 3b (93%),\textsuperscript{11b} also without the need for chromatographic purification (Scheme 2).

2-Aminobenzaldehyde (5a) could be obtained by oxidation of o-aminobenzyl alcohol.\textsuperscript{13a} Since 5a\textsuperscript{13b} was found to be an unstable compound that was prone to polymerization, the more stable derivatives 5b and 5c were chosen instead (Scheme 3). Imine 5b can be synthesized from protected nitrobenzaldehyde 8.\textsuperscript{13c,d} Reduction of this compound using sodium sulfide nonahydrate (Na\textsubscript{2}S·9H\textsubscript{2}O) in an ethanol–water mixture has been described,\textsuperscript{12} however, in our hands, this method was highly irreproducible (giving 5–65% yields) because of a tendency for the imine group to be hydrolyzed by the reagent. We noticed that by using anhydrous sodium sulfide as reducer in anhydrous ethanol, the reaction led to a 75% reproducible yield of amine 5b. However, sodium sulfide trihydrate (Na\textsubscript{2}S·3H\textsubscript{2}O) in anhydrous ethanol could also be utilized to give aminobenzaldehyde dimethyl acetal (5c)\textsuperscript{14a–d} in a 76% reproducible yield, starting from nitrobenzaldehyde dimethyl acetal (9).\textsuperscript{14} Compound 9 was produced quantitatively from nitrobenzaldehyde upon drying the azo trope (MeOH/CHCl\textsubscript{3}/H\textsubscript{2}O) with 3 Å molecular sieves.\textsuperscript{15} Compound 5c proved to be rather unstable; thus it was necessary to add a small amount of triethylamine during water washings and in the deuterated chloroform utilized while recording its NMR spectra. We used 5c as a crude compound since it often decomposed during vacuum distillation.\textsuperscript{14a–d}

The last step of the synthesis of 1b was a Friedländer condensation.\textsuperscript{16} This reaction is an acid or base catalyzed condensation, followed by a cyclodehydration between a 2-aminoarylaldehyde or ketone and a second carbonyl compound bearing a reactive \(\alpha\)-methylene group;\textsuperscript{17} many new procedures have been reported for this synthesis of quinolines.\textsuperscript{18} The reactivity of pyrrolidones 3, towards 2-aminobenzaldehyde was found to be quite dependent on the experimental conditions.\textsuperscript{8} Under basic catalysis, the cyclization predominantly gave the undesired heterocyclic nucleus 10\textsuperscript{8} (Scheme 4). Zalkow showed that the synthesis of 1a could be performed by refluxing 5a and ketone 3a in acetic acid (cat. H\textsubscript{2}SO\textsubscript{4}, reflux, 1 h, 30%) or, best, in a melt with \(p\)-toluenesulfonic acid (195–240 °C, 5 min, 88%).\textsuperscript{8} We applied these conditions to 5b or 5c and 3b, but the reactions proved to be very messy, giving black materials accompanied by many polymeric compounds. The same results were observed upon reflux in propanol (H\textsubscript{2}SO\textsubscript{4} or PTSA as catalyst). A recent paper described the use of a catalytic amount (5%) of sulfamic acid, in a melt at 70 °C, to perform Friedländer condensations.\textsuperscript{19} These conditions gave better yields of 1b than those utilized previously. We improved the yield and purity of 1b by using 5c (1 equiv), 3b (1.5 equiv) and sulfamic acid (1.5 equiv),

\begin{eqnarray*}
\text{Scheme 3} & \text{Reagents and conditions:} & i) \text{p-toluidine, EtOH, reflux, 30 min (95%);} & ii) \text{anhyd Na\textsubscript{2}S, EtOH, reflux, 5 min (75%);} & iii) \text{MeOH, CHCl\textsubscript{3}, MsOH, 3 Å MS, reflux, 24 h (100%);} & iv) \text{Na\textsubscript{2}S·3H\textsubscript{2}O, EtOH, reflux, 30 min (76%).}
\end{eqnarray*}
neat, at 150 °C for 10 minutes; unfortunately, the purification of obtained products was still rather difficult.

Friedländer reactions can also be realized by heating a ketone and an aromatic amino aldehyde in ethanol, with a catalytic amount of sulfuric acid and pyrrolidine as catalyst.20 In our hands, this method gave poor results; however, heating a mixture of ketone 3b (2 equiv), pyrrolidine (4 equiv) and methanesulfonic acid (MeSO3H; 0.7 equiv) in methanol–chloroform, whilst drying the ternary azeotrope (MeOH/CHCl3/H2O),12 led to quantitative formation of enamine 11. This intermediate was not isolated, but aminoacetal 5c (1 equiv) was added to the reaction mixture, and then the heating was continued for four days. A mixture of 1b and 10b (about 70:30, respectively, according to NMR) was thus obtained in 98% crude yield (Scheme 4). Isolation of 1b was achieved after basic hydrolysis of 10b, giving 12 in a manner similar to that described by Zalkow et al.5 Amine 12 (25%) was sufficiently pure for many uses, nonetheless, recrystallization of carbamate 1b gave the pure product in 65% yield.

In summary, our optimization of an old route8 has led to the development of a simple, four-step synthesis of methyl 1,3-dihydro-2H-pyrrolo[3,4-b]quinoline-2-carboxylate (1b), in 45% yield, from commercial starting materials. Our procedure could be compared to a recently described method21 whose yield was only 23–28% and which is described in the literature.11a

A mixture of ketone 3b, pyrrolidine (4 equiv) and methanesulfonic acid (MeSO3H; 0.7 equiv) in methanol–chloroform, whilst drying the ternary azeotrope (MeOH/CHCl3/H2O),12 led to quantitative formation of enamine 11. This intermediate was not isolated, but aminoacetal 5c (1 equiv) was added to the reaction mixture, and then the heating was continued for four days. A mixture of 1b and 10b (about 70:30, respectively, according to NMR) was thus obtained in 98% crude yield (Scheme 4). Isolation of 1b was achieved after basic hydrolysis of 10b, giving 12 in a manner similar to that described by Zalkow et al.5 Amine 12 (25%) was sufficiently pure for many uses, nonetheless, recrystallization of carbamate 1b gave the pure product in 65% yield.

Melting points were determined using an Electrothermal apparatus and are uncorrected. 1H NMR spectra were obtained on a Varian Gemini 2000 at 200 MHz. IR spectra were obtained in ATR mode on a FTIR Bruker Tensor 27 spectrometer. Microanalyses were performed by the Service de Microanalyses of LSEU, Université de Bourgogne, Dijon, France.

**Dimethyl 4-Oxo-1,3-pyridinidocarboxylate (2b)**

A stirred suspension of NaH (19 g, 0.792 M) in toluene (450 mL) was refluxed for 10 min, then heating was stopped and carbamate 4b13 (102.2 g, 0.714 M) was added slowly (2 h). The mixture was stirred at r.t. for 12 h then methyl acrylate (89.6 g, 1.040 M) in toluene (200 mL) was added and stirring was continued for 5 h. MeOH (100 mL) was added and the solvents were evaporated. HCl (34%, 250 mL) was added to the residue and the solution was extracted with EtOAc (10 × 100 mL) to give ester 2b (75%) with the same properties as described in the literature.12

**Methyl 3-Oxo-1-pyrroloidinecarboxylate (3b)**

A stirred mixture of ester 2b (45 g, 0.224 M) in HCl (34%, 5.3 mL) and H2O (125 mL) was refluxed for 15 h. After cooling, the solution was extracted with EtOAc (10 × 50 mL) and the organic phase was washed several times with sat. aq NaHCO3, then dried (Na2SO4) and evaporated to give ketone 3b (93%), with the same properties as described in the literature.11a

**N-(2-Aminobenzylidene)-p-toluidine (5b)**

A 2 L round-bottomed flask containing B2O3 (11.5 g, 47.8 mmol), anhydrous Na2S (6.2 g, 79.5 mmol), EtOH (100 mL) and a large magnetic stirring bar, was placed in a large oil bath at 100 °C. The mixture was stirred and refluxed for 5 min. After cooling to r.t., the mixture was poured into ice-water (300 mL) and the solid was filtered, washed with ice-water, then dried under vacuum (10−3 mmHg) to give nearly pure 5b (75%). The yellow solid was recrystallized from EtOH, then washed with heptane to give pure imine 5b (50%), with the same properties as described in the literature.12

**1-(Dimethoxyethyl)-2-nitrobenzene (9)**

A solution of 2-nitrobenzaldehyde (5a; 100 g, 0.66 M) and MsOH (2 g, 0.02 M) in CHCl3 (500 mL) and MeOH (1000 mL) was refluxed in a soxhlet-type apparatus containing 3 Å MS (150 g) for 24 h. After cooling to r.t., Et,N (10 g, 0.1 M) was added and the solvents were evaporated to give a quantitative yield of acetal 9, with the same properties as described in the literature.14c–e

**1-(Dimethoxyethyl)-2-aminobenzene (5c)**

Na2S·3H2O (100.5 g, 0.760 M) was added to a solution of 1-(dimethoxymethyl)-2-aminobenzene (5c) (25%) was sufficiently pure for many uses, nonetheless, recrystallization of carbamate 1b gave the pure product in 65% yield.

Melting points were determined using an Electrothermal apparatus and are uncorrected. 1H NMR spectra were obtained on a Varian Gemini 2000 at 200 MHz. IR spectra were obtained in ATR mode on an FTIR Bruker Tensor 27 spectrometer. Microanalyses were performed by the ‘Service de Microanalyses’ of LSEU, Université de Bourgogne, Dijon, France.

**1H NMR (200 MHz, CDCl3):** δ = 2.60 (t, J = 5 Hz, 2 H, CH2OCO), 3.85 (s, 3 H, CH3), 3.90 (t, J = 5 Hz, 4 H, CH2NCH2).

**Dimethyl 4-Oxo-1,3-pyridinidocarboxylate (2b)**

A stirred suspension of NaH (19 g, 0.792 M) in toluene (450 mL) was refluxed for 10 min, then heating was stopped and carbamate 4b13 (102.2 g, 0.714 M) was added slowly (2 h). The mixture was stirred at r.t. for 12 h then methyl acrylate (89.6 g, 1.040 M) in toluene (200 mL) was added slowly (2 h). The mixture was stirred at r.t. for 24 h then NaH (21 g, 0.875 M) and toluene (150 mL) was added and stirring was continued for 5 h. MeOH (100 mL) was added and the solvents were evaporated. HCl (34%, 250 mL) was added to the residue and the solution was extracted with EtOAc (10 × 100 mL) to give ester 2b (75%) with the same properties as described in the literature.12

**1H NMR (200 MHz, CDCl3):** δ = 3.65 (d, J = 9.5 Hz, 2 H, NCH2CH), 3.76 (s, 3 H, NCOCH3), 3.79 (s, 3 H, COOC2H5), 4.15 (d, J = 3.3 Hz, 2 H, NCH3CH2O), 4.23 (t, J = 3.3 Hz, 1 H, CHCO).

**Methyl 3-Oxo-1-pyrroloidinecarboxylate (3b)**

A stirred mixture of ester 2b (45 g, 0.224 M) in HCl (34%, 5.3 mL) and H2O (125 mL) was refluxed for 15 h. After cooling, the solution was extracted with EtOAc (10 × 50 mL) and the organic phase was washed several times with sat. aq NaHCO3, then dried (Na2SO4) and evaporated to give ketone 3b (93%), with the same properties as described in the literature.11a

**1H NMR (200 MHz, CDCl3):** δ = 2.60 (t, J = 5 Hz, 2 H, CH2OCO), 3.85 (s, 3 H, CH3), 3.90 (t, J = 5 Hz, 4 H, CH2NCH2).
The aqueous phase A was neutralized with HCl (1 M), extracted with CH2Cl2 (3× 150 mL), dried (Na2SO4) and evaporated. The residue obtained was recrystallized from Et2O to give amine 12 (25%), with the same properties as described in the literature.  

The combined organic phase B was washed with H2O (50 mL), made slightly acidic with HCl, then with alkaline H2O (50 mL), made slightly basic with NaHCO3, dried (Na2SO4) and evaporated. The residue obtained was recrystallized from Et2O to give carbamate 1b (65%).

Yellowish solid; mp 130–132 °C (EtOAc).

IR (neat): 1672, 1608, 1554, 1485 cm–1.

1H NMR (200 MHz, CDCl3): δ = 3.84 (s, 3 H, OCH3), 4.85–4.95 (m, 4 H, 2 × CH2), 7.55 (t, J = 7.5 Hz, 1 H, ArH), 7.72 (td, J = 7.5, 1.3 Hz, 1 H, ArH), 7.82 (d, J = 8.0 Hz, 1 H, ArH), 7.85 (m, 2 H, 2 × ArH).

Anal. Calcd for C13H12N2O2: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.15; H, 5.28; N, 12.25.

References


(10) The same reaction performed with metallic sodium is less effective.  


(15) Apple, I. A.; Meth-Cohn, O. ARKIVOC 2002, (vi), 4; and references cited therein.


(22) More than 50 g of compound 1b has been easily synthesized using this method.